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Dosimetry of Ozone and Nitrogen Dioxide in Man and Animals

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Introduction

The health effects of ozone (O_3) and nitrogen dioxide (NO_2) are assessed from animal toxicological, controlled human, and epidemiological studies. These assessments will be strengthened when results of animal studies can be quantitatively extrapolated to man. To achieve quantitative extrapolation, improvements are needed in the areas of dosimetry and species sensitivity. And, of course, an adequate health effect data base must exist on which to make extrapolations.

The focus of this paper is to review the regional dosimetry of O_3 and NO_2 in the respiratory tract of man and animals. Dosimetry relates to estimating the amount of pollutant reaching a specific target region of the respiratory tract as a function of exposure concentration. At present, there are two approaches to dosimetry, experimental and mathematical modeling, which will be discussed.

Experimental Studies of Respiratory Tract Absorption

Animal experiments have been carried out to obtain direct measurements of O_3 and NO_2 absorption; however, experimentally obtaining local lower respiratory tract (tracheobronchial and pulmonary regions) uptake data is currently extremely difficult. Nevertheless, experimentation is important in assessing concepts and hypotheses, and in validating mathematical models which can be used to predict local doses. There are only a few studies in which experimental measurements of the absorption of O_3 or NO_2 have been made, and of these few, most have dealt with nasopharyngeal absorption.

Table I gives the results of various O_3 studies and clearly demonstrates that there are species differences in the nasopharyngeal absorption of O_3. For example, with exposure to 1960 $\mu g/m^3$ (1 ppm), nasopharyngeal removal varies from about 50 percent in the rabbit and guinea pig[1] to almost 100 percent in the dog.[2] The concentration of O_3 reaching the trachea depends heavily upon the route of breathing, as demonstrated by studies in dogs.[3] Also, one can infer from the work of Moorman et al.[4] using dogs that chronic exposure to environmentally relevant O_3 levels should not result in tracheal O_3 concentrations significantly greater than those observed with acute exposure.

Less experimental data are available for NO_2 removal in the respiratory tract.[5-8] Corn and coworkers[5] determined the mass transfer of NO_2 in the upper portion of the conducting airways in cats for a variety of breathing frequencies and tidal volumes. The mass transfer coefficient, K_G, varied from 1.8×10^{-6} mol/cm^2 s mmHg for 10.3 mg NO_2/m^3 (5.5 ppm) to 1.55×10^{-6} mol/cm^2 s mmHg for 4.1 mg NO_2/m^3 (2.2 ppm), indicating K_G was not sensitive to changes in the concentration of NO_2. K_G was also not found to vary with frequency or depth of breathing. In Rhesus monkeys, Goldstein et al.[6] demonstrated that 50 to 60% of the pollutant was retained during quiet respiration of NO_2 levels ranging from 0.56 to 1.71 mg/m^3 (0.3 to 0.91 ppm). Exposing human volunteers to NO_2 levels ranging from 0.94 to 9.4 mg/m^3 (0.5 to 5 ppm), Von Nieding et al.[8] found that 80 to 90 percent of the inhaled NO_2 was retained.

Mathematical Dosimetry Models

The major factors affecting the uptake of gases in the respiratory tract are the morphology of the respiratory tract, the route of breathing, the depth and rate of breathing, physicochemical properties of the gas, the physical processes which govern gas transport, and the physicochemical properties of the aqueous material on the surface of the airways or gas exchange units. Because the factors affecting the transport and absorption of O_3 and NO_2 are general to all mammals, a given model, using appropriate species and/or disease-specific anatomical and ventilatory parameters, can be used to describe pollutant absorption in the species, as well as in different sized, aged, or diseased members of the same species. Models may also be used to explore processes or factors which cannot be studied experimentally, to identify areas needing additional research, and to test our understanding of O_3 and NO_2 absorption in the respiratory tract.

LaBell et al.[9] developed a model for the absorption of gases in the nasal passages using chemical engineering device parameters to correspond to various biological parameters of rats. Their model predicts 99 percent penetration of O_3 through the nasal passages. This large discrepancy with experimental data[1,3] is probably because the model does not account for reactions of O_3 with mucus and epithelial tissue. A model for uptake of vapors by the nose was developed[10] based on the assumption of quasi-steady state flow, mass balance, and that the flux of a trace gas at the air-mucus interface is proportional to the gas phase partial pressure of the trace gas and a "local uptake coefficient." Aharonson et al.[10] applied the model to O_3 uptake data of Yokoyama and Frank[3] and concluded that the uptake coefficient (average mass transfer coefficient) for O_3 increases with increasing air flow rate.

There are two models[11,12] for which published results are available for the absorption of O_3 in the lower respiratory tract of man. Although never formally published, the major features of the model of McJilton et al.[11] have been discussed and simultation results for O_3 absorption in each generation of the human lung have been presented.[13,14] In addition to the human lung, Miller[12] modeled the absorption of O_3 in the lungs of animals. Results of simulations of the respiratory tract absorption of ozone in humans, rabbits, and guinea pigs are available.[12,15,16]

In both the McJilton et al. and Miller models, the descriptions of ozone transport and absorption in the lumen are based on a one-dimensional differential equation relating axial convection, axial dispersion or diffusion, and the loss of ozone by absorption at the gas-liquid interface. However, there are major differences in the two models. Ozone is known to react chemically with constituents of the liquid lining. This factor was not included in the McJilton et al. model. Miller and co-workers took into account the reaction of ozone with the unsaturated fatty acids (UFA) and amino acids in the mucous-serous lining. Reactions of ozone with other components (such as carbohydrates) were not included in the model because of insufficient information.[12,15] The ozone-UFA and ozone-amino acid reactions were assumed fast enough so that an instantaneous reaction scheme based on

that outlined in Astarita[17] could be used. The inclusion of chemical reactions results in significant differences between the tissue dose pattern curves in the tracheobronchial region predicted by the two models. The McJilton et al. model predicts a dose curve in the conducting airways that decreases distally to the 13th or 14th generation from a maximum at the trachea.[11,13,14] By contrast, the Miller model predicts the tissue dose to be a minimum at the trachea and to increase distally to the pulmonary region.[12,15,16]

Although the instantaneous reaction scheme is a good preliminary approach, its use is not completely justifiable in treating all the various O_3 reactions in the mucous-serous lining. Second-order rate constants of ozone with some of the mucous UFA indicate that while they are large,[18] they are less than the diffusion-limited rates necessary for the instantaneous reaction scheme. Although experimental evidence[19] suggests that the reactions of O_3 with amino acids are very rapid, rate constants for these reactions, as well as for others, are not known. Thus, the information available is scanty, making the the specification of a reaction mechanism or reaction scheme difficult and assumptions necessary.

While it appears that NO_2 should react with many of the same constituents of the liquid layers lining the lungs as does O_3, even less is known for specifying the appropriate reaction scheme to model NO_2 absorption. Definitive studies are critically needed on the types and rates of reaction of NO_2 with various free amino acids, lipids, carbohydrates, etc. In recognition of these various uncertainties, Miller et al.[20] modeled the absorption of NO_2 in animals and man by assuming for NO_2 the same mucous production scheme they had used for O_3, but one-half of the O_3 reactant production rates. Also, recognizing the unknown reactivity of NO_2, they examined the sensitivity of the predicted tissue dose to various values of NO_2 reactant production rates.

Predicted Absorption of O_3 and NO_2 in the Lower Respiratory Tract Using the Miller Model

Simulations of O_3 and NO_2 absorption in different animals and man can be carried out by modifying input parameters of the computer program that solves the mathematical equations. These input parameters, which characterize a species, include the number and dimensions of the airways, tidal volume, and breathing frequency. For the analyses presented her, the morphometric data of Kliment[21] were used for rats, rabbits, and guinea pigs, while the data for man are from Weibel.[22]

Simulation results for absorption of NO_2 in the lower respiratory tract of man are illustrated in Figure 1. While the figure focuses on NO_2, O_3 absorption is also depicted since the curve for 1 K_o corresponds to the reference reaction production rate for O_3 and since 9628 atmos./mole fraction for Henry's law constant (H) is very similar to that of O_3 (H = 9800 atmos./mole fraction). The factor in front of K_o refers to the fraction of K to which the reactant production rate has been reduced. Thus, the results are plotted of what may be considered extremes for the uptake of NO_2 - no chemical reactions ($0K_o$) and an upper limit, as represented by the O_3 rate ($1k_o$).

The patterns for the loss of pollutant from the lumen of the airway (Figure 1A) and for tissue absorption (Figure 1B) illustrate important aspects of the dosimetry of O_3 and NO_2. For physical absorption ($0K_o$) the quantity/unit area lost from the lumen of conducting airways is the same as that delivered to the tissue so that the mucous-serous lining offers the tissue no protection from oxidant injury. Variation in the uptake of NO_2 in the trachea is 5-fold between the extremes of physical absorption and instantaneous reaction. These differences persist for about 10 generations. The variation in oxidant uptake becomes less pronounced in the distal portions of the conducting airways and is nonexistant in the terminal bronchioles (generation 16). Further, as Figure 1A shows, for NO_2 and has been previously shown for O_3,[15] uptake in the gas-exchange regions of the lung (generations 17-23) is not sensitive to the variations in oxidant reactant production rates. This is due in large part to the modeling assumption of no chemical reactions between various components of surfactant, which lines the gas-exchange regions, and the oxidant gases, O_3 and NO_2.

The presence of chemical reactions results in only a fraction of the gas lost by the lumen reaching the tissue (curves $.5K_o$ and $1K_o$ of Figure 1B). The protective nature of the mucous-serous layer can be seen by comparing Figures 1A and 1B. With the chemical reaction schemes modeled, no NO_2 or O_3 reaches the tissue until the distal portion of the conducting airways.[3] That the lack of penetration of the gas is indeed protective must await toxicological investigation since the reaction products may themselves also be toxic. The peak tissue dose for both O_3 and NO_2 is predicted to occur in the first generation of respiratory bronchioles (generation 17). The rapid fall in tissue dose in the alveolar region (generations 20-23) is largely due to the correspondingly rapid increase in lung surface area.

Predicted tissue doses in the lungs of rats, rabbits, and guinea pigs for a tracheal NO_2 concentration of 800 $\mu g/m^3$ are given in Figure 2. The morphometric data[21] used to obtain these dose curves are classified according to morphometric "zone" rather than by airway generation, as was the case for man,[22] so that several human airway generations may correspond to a morphometric "zone" in these animal species. Also, a value of 0.5 K_o was used for the simulations given in Figure 2.

The tissue dose curves for the guinea pig and rabbit are relatively similar. As evidenced in Figure 2, the curves for both of these animal species differ from the rat tissue dose curve with respect to shape and location of the maximal dose. The tissue dose curve for rats is flatter over major portions of the tracheobronchial tree, and alveolar ducts are predicted to be the region of maximal NO_2 tissue dose, whereas the maximal dose region is the last generation of bronchioles in the other animal species. This shift reflects the transition from mucous lined to surfactant lined regions of the lung relative to the model formulation concerning chemical reactions of NO_2 with constituents of the liquid lining layer.

The animal dose curves of Figure 2 can be compared to the human dose curve for 0.5 K_o in Figure 1B, keeping in mind the following approximate relationship between morphometric "zone" and generation:

zones 0-4 relate to human generations 0-11, zones 5 and 6 correspond to generations 12 through 19, zone 7 refers to generations 20-22, and zone 8 corresponds to generation 23. In all three animal species, as well as in man, the peak tissue dose of NO_2 and of O_3,[15] occurs in the first surfactant-lined zone or generation. The junction of the conductive and respiratory zones has been shown to be the region of maximal lower respiratory tract damage in animals exposed to O_3.[23,24] Significant damage in this region is also associated with exposure to NO_2.[25]

Summary

Agreement between experimental data on maximum morphological damage and maximal predicted tissue doses offers promise that mathematical dosimetry models can contribute to a better understanding of effective doses in animal studies and their correspondence to human exposure levels. Modeling must be a dynamic process to take advantage of new information and evolving conceptualizations of physical, chemical, and biological processes. Qualitative extrapolations from animals to man have been used indirectly in setting National Ambient Air Quality Standards. Continued development of dosimetry models, along with information on species differences in sensitivity to pollutants, have the potential to make extrapolations between animals and man more quantitative in the future.

Table I Experimental Data on the Uptake of O_3 in the Respiratory Tract

Region	Species	Exposure Level (ppm)	Route of Airflow	Flow Rate (l/min)	Uptake (percent)	Reference
Nasopharynx	Dog	0.2 -0.4	Nose	3	100	Vaughn et al.[2]
	Dog	0.26-0.34	Nose	3.5-6.5	72	Yokoyama and Frank[3]
				35-45	37	
			Mouth	3.5-6.5	34	
				35-45	12	
		0.78-0.8	Nose	3.5-6.5	59	
				35-45	27	
			Mouth	3.5-6.5	27	
				35-45	9	
	Dog	1	Nose	3	97-99	Moorman et al.[4]
		3		3	76[a]	
				3	96[b]	
	Rabbit	0.1-2.0	Nose	1	50.8-(4.1/x)[c]	Miller et al.[1]
	Guinea Pig	0.1-2.0	Nose	0.16	52.2+(3.7/x)[c]	Miller et al.[1]
		2-3		0.16	58-61	
Lower Respiratory Tract	Dog	0.2-0.4	Tracheal Cannula	2.5-4.2	87	Yokoyama & Frank[3]
				3.8-6.3	83	
		0.7-0.85	Tracheal Cannula	2.5-4.2	84	
				3.8-6.3	80	

[a] Chronically exposed
[b] acutely exposed
[c] Exposure level = X

Figure Captions

Figure 1. A. NO_2 lost by the airway for various lumen reactant production rates as a function of airway generation in the human lung. B. Predicted NO_2 tissue dose curves in the lungs of man for various reactant production rates. Simulations used a tidal volume of 500 ml and a respiratory frequency of 15 breaths/min. From Miller et al.[20]

Figure 2. Predicted NO_2 tissue dose curves in the lungs of rats, guinea pigs, and rabbits for various morphometric regions. For rats, guinea pigs, and rabbits, tidal volumes of 0.95, 1.8, and 21 ml and breathing frequencies of 105, 90, and 50 breaths/min., respectively were used. Alveolar ducts and sacs are represented by A.D. and A.S., respectively. Adapted from Miller et al.[20]

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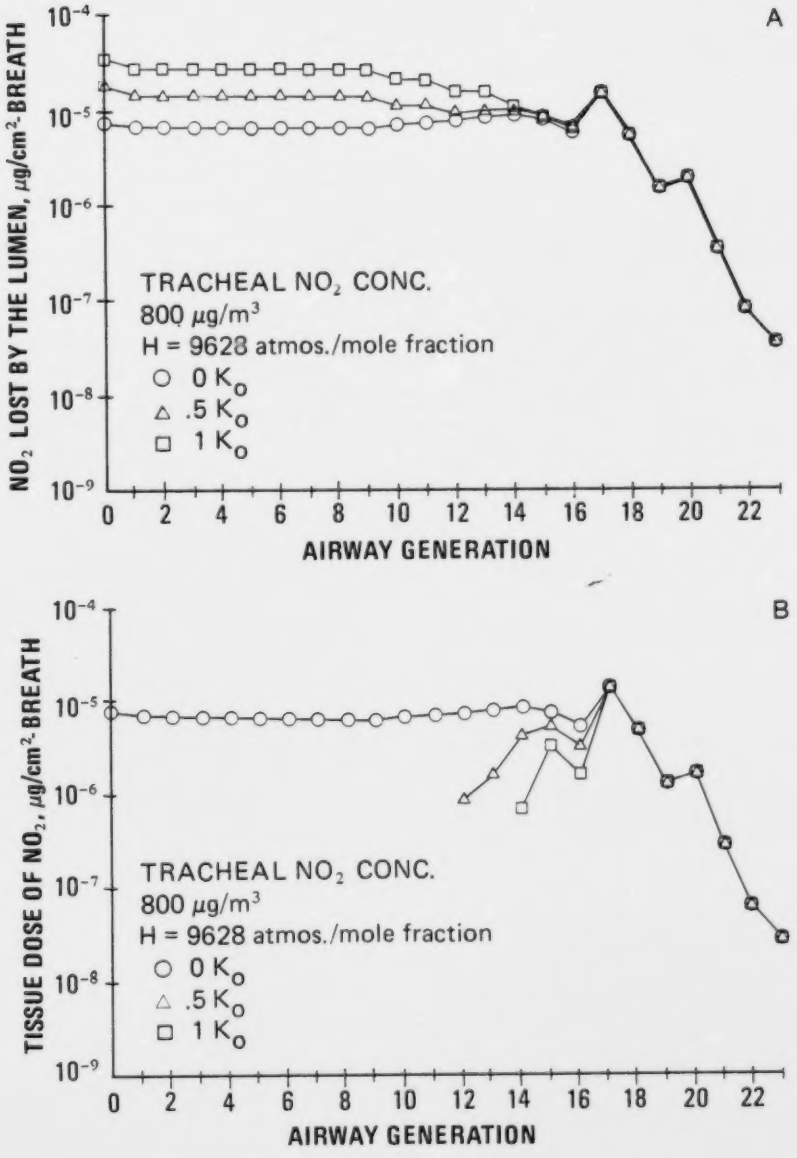
A
NO_2 LOST BY THE LUMEN, $\mu g/cm^2$-BREATH
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
10^{-9}
TRACHEAL NO_2 CONC.
800 $\mu g/m^3$
H = 9628 atmos./mole fraction
○ 0 K_o
△ .5 K_o
□ 1 K_o
0 2 4 6 8 10 12 14 16 18 20 22
AIRWAY GENERATION
B
TISSUE DOSE OF NO_2, $\mu g/cm^2$-BREATH
10^{-4}
10^{-5}
10^{-6}
10^{-7}
10^{-8}
10^{-9}
TRACHEAL NO_2 CONC.
800 $\mu g/m^3$
H = 9628 atmos./mole fraction
○ 0 K_o
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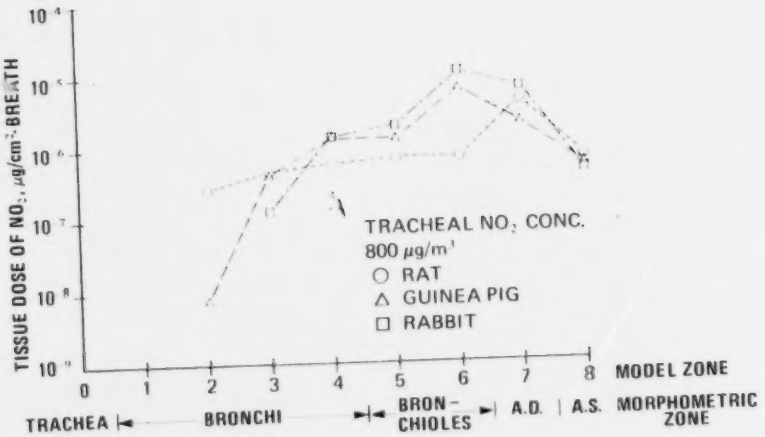
□ 1 K_o
0 2 4 6 8 10 12 14 16 18 20 22
AIRWAY GENERATION


TISSUE DOSE OF NO2, μg/cm2-BREATH
10 4
10 5
10 6
10 7
10 8
10 9
TRACHEAL NO2 CONC.
800 μg/m3
○ RAT
△ GUINEA PIG
□ RABBIT
0 1 2 3 4 5 6 7 8 MODEL ZONE
TRACHEA
BRONCHI
BRON-CHIOLES
A.D.
A.S.
MORPHOMETRIC ZONE